

REMARKS

Applicant respectfully requests reconsideration. Claims 1-4, 6, 8-13 and 18-57 were previously pending. Claim 48 is now cancelled without prejudice or disclaimer, and claims 1, 6, 20, 29, 30, 31, 32, 49 and 55-57 are now amended. Support for these amendments can be found in the claims as originally filed and/or previously pending and in the specification at least on page 28 line 31 through to page 29 line 5 and page 29 line 29 through to page 30 line 7. As a result, claims 1-4, 6, 8-13, 18-47 and 49-57 are pending, with claims 1-4, 6, 8-12, 18, 21, 23-36, 38-46, 50-57 being under examination. No new matter has been added.

Claim Objection

Claim 31 was objected to due to the recitation of “mirror images”. The claim has been amended to refer to “mirror image peaks”. Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §101

Claims 1-4, 6, 8-12, 18, 21, 23-46 and 50-57 are rejected under 35 U.S.C. § 101 because according to the Examiner the claimed invention is directed to non-statutory subject matter.

The Examiner has stated that, in order to encompass statutory subject matter, the claimed process must include a step of physical transformation or it must produce a useful, concrete and tangible result. Respectfully, Applicant notes that, since the issuance of the instant Office Action, the “machine-or-transformation” test has been held to be the correct test of patentable subject matter rather than the useful, concrete and tangible result test. In re Bilski, 545 F.3d 943, 88 U.S.P.Q.2d 1385 (Fed. Cir. 2008).

The claims have been amended to recite that the individual intensity profiles are obtained by exposing polymers to an energy source and detecting signals from such polymers using an electromagnetic detection system. These polymers are labeled with sequence-specific probes, and it is the signals from such probes that are detected by the electromagnetic detection system. Support for these amendments can be found in the specification at least at page 28 line 31 through to page 29 line 5 and page 29 line 29 through to page 30 line 7. Accordingly, the claims recite the specific machinery that is required for the claimed invention, and they therefore meet the “machine-or-transformation” test set forth in Bilski.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §112

Claims 1-4, 6, 8-12, 18, 21, 23-46 and 50-57 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 29, 30, 32 and 55-57 have been amended to address the inconsistency identified by the Examiner relating to individual intensity profiles.

Claim 56 has been amended to clarify and distinguish between “peaks” recited in the claims.

Claim 32 has been amended to address the lack of antecedent basis identified by the Examiner.

As a result of these amendments, these claims and those that depend from them are considered definite. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Taylor, Chan, Chan et al. and Sun

Claims 1-4, 6, 8-12, 16-18, 21, 23-25, 26, 28, 44-45, 50-53 and 55-56 are rejected under 35 U.S.C. §103(a) as being unpatentable over Taylor et al. (PG PUB 2003/0082538, hereinafter “Taylor”), in view of Chan (WO 98/35012, hereinafter “Chan”), in view of Chan et al. (US PG PUB 2002/0039737, hereinafter “Chan et al.”) and in view of Sun (Pattern Recognition Letters Vol. 16, p 987-996, 1995).

A prima facie case of obviousness requires the showing of a motivation or reason to modify or combine reference teachings, a reasonable expectation of success relating to such modification or combination, and each and every limitation of the rejected claims. The Examiner has not met this burden as shown below and thus a prima facie case has not been made.

Taylor reports a method for analyzing chromatographic profiles of nucleic acid samples. Individual peaks in these profiles represent entire double stranded nucleic acid molecules. If multiple peaks exist in the profile, these are indicative of different nucleic acid duplexes. Such

duplexes may be homoduplexes, heteroduplexes, or a mixture of both. Each starting profile is a population profile, with each peak representing the time at which a particular nucleic acid duplex elutes (in its entirety). Taylor does not obtain individual intensity profiles from individual labeled polymers, as recited in the rejected claims. Instead Taylor obtains a population profile in which every eluted nucleic acid duplex generates a single rather than multiple peaks. Since each nucleic acid duplex gives rise to only one peak in a profile, there is no directionality to any of the profiles of Taylor. As a result, the problem being solved by the method of the rejected claims (i.e., distinguishing between “head-first” and “tail-first” individual polymer profiles) does not even exist in the dataset used by Taylor.

Since Taylor does not obtain individual profiles, it cannot teach manipulation of such individual profiles to generate sample population profiles. Specifically, Taylor cannot teach (a) aligning individual intensity profiles with respect to an alignment reference point (which may or may not be a center of molecule reference point), (b) combining aligned individual intensity profiles to generate a sample population profile, (c) selecting a peak in the sample population profile and obtaining individual intensity profiles that contribute to the peak, (d) generating peak profiles, and/or (e) comparing peak profiles to sample population profiles.

The Examiner has misread Taylor and concluded that various limitations of the rejected claims are disclosed by the reference. For example, the Examiner states that the profiles in Taylor are aligned with respect to an alignment reference point, referring to Fig. 16. Fig. 16 shows a number of overlapped sample profiles as well as four markers that are arbitrarily chosen as described in [0222]. There is no teaching in Taylor that the sample profiles, of which there are many in Fig. 16, are aligned based on the position of these markers. Thus, Taylor does not teach an alignment reference point which is used to align individual polymer profiles in order to generate a sample population profile. Significantly, the markers in Fig. 16 also cannot be center of molecule reference points because the profile is not a profile of labels on an individual polymer (i.e., there is no center of molecule reference point in the profiles of Taylor). The Examiner further states that Fig. 16 and 17 show averaged profiles, however both Figures actually show a plurality of overlapped profiles rather than a single averaged profile.

Taylor also does not teach how nucleic acids of varying length can be analyzed according to its methods. The reference concedes that nucleic acids of varying size will elute at different

times. If Taylor were to use nucleic acids of different size, it would be unclear whether the different elution times would be the result of a difference in length of the duplex or the presence of a polymorphism. It is for this reason that Taylor teaches using a population of DNA fragments that are assumed to have the same length. (See [0164].) To be clear, Taylor does not teach size separation of the sample prior to alignment, as alleged by the Examiner. The passage cited by the Examiner for this teaching intends instead to draw the distinction between the use of MIPC and DMIPC, only the latter of which is the method of Taylor.

Taylor also does not teach labeling the nucleic acids with sequence-specific probes, as required by the rejected claims, and as acknowledged by the Examiner. Although the Examiner points to paragraph [0156] as evidence of “labeled” nucleic acids, this text describes detection of UV and fluorescent signals, neither of which is evidence of the use of sequence-specific probes.

The Examiner concedes that Taylor does not teach sequence-specific probes and an alignment reference point that is a center of molecule reference point. However, the Examiner relies on Chan for these teachings. Chan provides a method for analyzing single polymers having one or more labels positioned along their length. The profiles generated by Chan therefore correspond to individual polymers with peaks within each profile corresponding to labels in the polymer. The Examiner states that sequence-specific probes of Chan could be used in the method of Taylor because

“Chan shows by doing so the polymers labeled with sequence specific probes have a characteristic signature that allow the polymers to be identified from mixtures of similar polymer of different sequence”.

It is unclear what result is achieved by analyzing the polymers of Chan using the methods of Taylor. The characteristic signature of Chan refers to an individual polymer profile that contains peaks corresponding to labels on the polymer. The characteristic signature of Taylor is an elution time relative to other nucleic acids in a sample, and more specifically relative to nucleic acids in the sample that differ in a single nucleotide position. There is no rationale for combining the two approaches at least because they acquire different polymer data, and they analyze such polymer data differently in order to obtain different polymer information. In view of these differences and the foregoing arguments, there is also no reasonable expectation of success relating to this combination.

With respect to the center of molecule reference point, the cited passage in Chan (page 63 lines 25-31) refers to end-labeling of polymers (“The nucleic acid is end-labeled to provide a reference point ...”), not a center of molecule reference point. The other cited passage (page 76 lines 2-3) refers to a polymer specific feature relating to the sequence of the polymer. The Examiner asserts that these teachings provide the basis for a center of molecule reference point because the instant specification does not define the term and it can therefore be given its broadest reasonable interpretation. To the contrary, Figs. 1 and 2 of the instant specification illustrate the center of molecule reference point, the Figure Legends provide a description of the use of the center of molecule reference point, and the specification further states

“More preferably, it is the center of the molecule (or center of the polymer). The center of the molecule can be determined by labeling the polymer uniformly along its length with for example a length proportional dye or stain, estimating the length of the polymer based on the length of the intensity profile and thereby determining the midpoint or center of the molecule.” (page 10, lines 26-31.)

Based on these combined teachings in the specification, one of ordinary skill in the art would understand the meaning of the term and could not reasonably conclude that an end-label reference point is a center of molecule reference point. Moreover, a polymer specific feature as defined by Chan is dependent upon the particular sequence of the polymer and, by its very definition, must be specific to the polymer. A center of molecule reference point is not sequence dependent and is present in every analyzed polymer and thus cannot be specific to any particular polymer.

The Examiner has asserted that Chan provides a number of other teachings but these assertions are not supported by the citations provided. For example, the Examiner cites passages at page 15 lines 15-16 for the teaching of a reference point that is an internal reference point and a reference point that is a sequence-specific probe. The passage actually states that “The method ... is a method for identifying a unit specific marker of the polymer, the identity of the unit specific marker being indicative to the identity of at least one unit of the polymer.” There is no mention of a reference point. Other passages that do not support the Examiner’s statements are cited in the instant Office Action as page 63 lines 18-24, page 119 line 35, page 40 lines 24-26, and page 40 line 31. The Examiner is asked to review these cited passages and correct the citation or provide other evidence of the limitations.

Chan et al. also relates to analysis of polymers having labels attached thereto. One of the cited passages in Chan et al. reports analysis of end-labeled polymers by measuring the time taken for the ends of a polymer to travel between two detection zones. The passage contemplates that a polymer may travel into the detection zones in either a head-first or a tail-first direction, provided that if it is labeled only on one end it cannot change orientation during travel. Accordingly, the data analysis performed by Chan et al. is insensitive to the directionality of the polymer as it travels through the detection zone. Chan et al. provides no motivation to manipulate a non-oriented dataset in order to orient individual intensity profiles within the set.

The Examiner makes the unsupported statement that “Chan et al. suggest that a profile of a single polymer may produce two signal amplitude profiles that are mirror images dependent on which end of the polymer enters the detection zone as the leading edge.” The Examiner is asked to provide the basis in Chan et al. for this teaching.

There is no basis for combining the teachings of Taylor with Chan et al. at least because Taylor generates and analyzes overlaid sample profiles each having peaks that correspond to entire single polymers while Chan et al. generates individual polymer profiles each having peaks that correspond to labels on individual polymers. Moreover, Taylor seeks to identify nucleotide polymorphisms in a population of nucleic acids while Chan et al. seeks to determine length and/or velocity of a polymer by labeling one or both of its ends and tracking its movement through one or more detection zones.

The Examiner further relies on Sun for the teaching of symmetry detection. More specifically, the Examiner states that “if half of an image is mirror image of the other half, then one half need not be described suggesting flipping or inverting”. Applicant respectfully points out that the rejected claims relate to methods in which entire profiles of individual polymers are known (i.e., both halves are known). These methods are directed in part at identifying individual profiles that are mirror images of each other rather than creating a full profile based only a known half profile. Accordingly, the relevance of Sun to the claimed methods is unclear and its combination with Taylor, Chan and Chan et al., none of which report data corresponding to only a single half of a polymer, is improper.

For at least the reasons set forth above, no prima facie case of obviousness exists in view of Taylor, Chan, Chan et al. and Sun. There exists no rationale for combining the references as

suggested by the Examiner at least because of the disparate datasets each obtains, the manipulation each contemplates, and the end result each is achieving. There is no reasonable expectation of success relating to such combination at least because of the unpredictable manner in which the disparate datasets would be analyzed. And finally, even if the combination could be made, each and every limitation of the rejected claims is not provided as outlined above. Reconsideration and withdrawal of this rejection is respectfully requested.

Taylor, Chan, Chan et al., Sun and Schwartz

Claims 1, 27, 29-36, 38, 46 and 57 are rejected as being unpatentable over Taylor, in view of Chan, Chan et al. and Sun as applied to claims 1-4, 6, 8-12, 16-18, 21, 23-25, 26, 28, 44-45, 50-53, and 55-56 above, and further in view of Schwartz et al. (Science, Vol. 262, No. 5130, p. 110-114, 1993, hereinafter Schwartz).

The lack of a prima facie showing in view of Taylor, Chan, Chan et al. and Sun is discussed above. The Examiner states that this combination does not “explicitly show that a peak profile that resembles a population profile is a non-oriented profile”. Applicant maintains, as presented above, that there is no reason to combine the references and that there is no reasonable expectation of success relating to such combination, particularly in view of the disparate datasets and results obtained by each of the reference methods. Moreover, the combination, even if proper, does not yield a method that obtains and manipulates individual intensity profiles from individual labeled polymers including aligning the individual profiles with respect to an alignment reference point (whether or not it is a center of molecule reference point), combining aligned individual intensity profiles to generate a sample population profile, selecting peaks in the sample population profile and obtaining individual intensity profiles that contribute to such peaks, and/or comparing such peak profiles with the sample population profile. Schwartz does not cure these deficiencies.

Schwartz reports a method for determining restriction maps for yeast chromosomes. These nucleic acids are cut by restriction enzymes and the resulting fragments are optically imaged to determine length. The nucleic acids are not labeled with sequence-specific probes, and no individual intensity profiles are generated having peaks corresponding to labels on the nucleic acids. With respect to symmetry, Schwartz states that “DNAs that have nearly

symmetrical maps cannot be optimally averaged to improve resolution unless one end is identified, so that map polarity must be established through ancillary means.” (See page 113, first column, second full paragraph.) In other words, Schwartz requires that the nucleic acid fragments be oriented either by one end labeling or through other means in order to be useable. Schwartz therefore teaches away from the use and manipulation of non-oriented polymers and datasets, and therefore teaches away from the methods of the rejected claims.

Notwithstanding the foregoing, Applicant particularly addresses various statements made the Examiner. First, the Examiner’s statement that “The suggestion by Schwartz et al. to establish polarity or generate an oriented profile” and the symmetric nature of nucleic acid which prevents optimal averaging (i.e., “non-oriented profile”) read on the determining and generating oriented and non-oriented profiles” is unsupported. Schwartz acknowledges that a restriction map of a given nucleic acid may be symmetrical and it further states in that in these instances the polarity of the map will have to be determined in order to average such maps for the purpose of improving resolution. Schwartz contemplates that polarity may be established by labeling one end of the nucleic acid. Such an approach will yield oriented nucleic acids without the need for manipulation of non-oriented datasets. Although Schwartz further acknowledges that in the absence of end-labeling “ancillary means” must be used to establish polarity of a map, the reference provides no insight as to what such ancillary means are. Thus, Schwartz adds nothing to the combination of references apart from identifying that polarity (or lack thereof) in nucleic acid maps is problematic and that single end labeling may be used to establish polarity.

Second, the Examiner states that “the elongated polymers described in Taylor et al., Chan, and Chan et al. are symmetrical objects that have at least one axis of symmetry that lies at midpoint of the length”. This statement is incorrect. Nucleic acids, including the nucleic acids of Taylor, Chan and Chan et al., are not inherently symmetrical. Moreover, the profiles generated by the methods of Taylor, Chan, and Chan et al. are also not inherently symmetrical. As an example, the profiles of Taylor are chromatograms showing elution times for nucleic acid duplexes in a sample. There is no symmetry in these plots at least because each peak represents a different entity.

Third, the Examiner states that the rejected claims are obvious because “techniques of inversion or “reflection”, combination and comparison of spectra, the identification of oriented

vs. non-oriented peak profile was recognized as part of the ordinary capabilities of one skill in the art.” This statement too is unsupported. None of the references cited by the Examiner shows these elements nor has any other evidence been made of record by the Examiner that establishes that such techniques were known at the time of filing. The Examiner’s conclusory statements rely on an improper reading and understanding of the reference teachings.

The Examiner is asked to provide evidence supporting these statements or otherwise reconsider the basis of the rejection.

For at least these reasons, the combination of Taylor, Chan, Chan et al., Sun and Schwartz does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Taylor, Chan, Chan et al., Sun and Dousseau

Claims 1, 28, and 39 are rejected as being unpatentable over Taylor, in view of Chan, Chan et al., and Sun as applied to claims 1-4, 6, 8-12, 16-18, 21, 23-25, 26, 28, 44-45, 50-53, and 55-56 above, and further in view of Dousseau et al. (Applied Spectroscopy, Vol. 43, No. 3, p 538-54, 1989, hereinafter Dousseau).

The lack of a prima facie showing in view of Taylor, Chan, Chan et al. and Sun is discussed above. The Examiner states that this combination does not “explicitly show the subtraction of spectra”. Applicant maintains, as presented above, that there is no reason to combine the references and that there is no reasonable expectation of success relating to such combination, particularly in view of the disparate datasets and results obtained by each of the reference methods. Moreover, the combination, even if proper, does not yield a method that obtains and manipulates individual intensity profiles from individual labeled polymers including aligning the individual profiles with respect to an alignment reference point (whether or not it is a center of molecule reference point), combining aligned individual intensity profiles to generate a sample population profile, selecting peaks in the sample population profile and obtaining individual intensity profiles that contribute to such peaks, and/or comparing such peak profiles with the sample population profile. Dousseau does not cure these deficiencies.

Dousseau teaches the subtraction of water from the transmission infrared spectra of aqueous solutions of proteins. The Examiner considers that “it would have been obvious to one

of ordinary skill in the art to modify the method of polymer analysis” of Taylor, Chan, Chan et al. and Sun “with the profile subtraction of Dousseau because “the process has the advantage of eliminating user bias encountered with interactive methods and takes into account baseline variations due to instrument drift.” Respectfully, the Examiner is suggesting that a water profile be subtracted from the profiles of Taylor, Chan, or Chan et al. Rejected claim 39 recites subtracting the peak profile, not a water profile, from the sample population profile. The combination of these references with Dousseau therefore does not yield the limitations of at least this claim. Moreover, there is no reason for combining the water subtraction method of Dousseau with the other references. Dousseau subtracts the water spectra in order to reduce noise and overcome user bias. There is no teaching in Taylor, Chan, or Chan et al. that signals are even detected from water and/or that any user bias exists in the method. In addition, subtraction of a peak profile from a sample population profile serves to subtract polymer profiles from a population profile rather than noise.

Therefore there exists no motivation or rationale for combining the references, no reasonable expectation of success in such combination (particularly given that there is no indication that water signals or spectra are a problem in the methods of Taylor, Chan, Chan et al. and Sun), and the combination even if made properly does not result in each and every limitation of the rejected claims. For at least these reasons, the combination of Taylor, Chan, Chan et al., Sun and Dousseau does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Taylor, Chan, Chan et al., Sun, Schwartz and Dousseau

Claim 40-41 and 54 are rejected as being unpatentable over Taylor, in view of Chan, Chan et al., Sun, and Schwartz as applied to claim 3-36, 38, and 46 above, and further in view of Dousseau.

The lack of a prima facie showing in view of Taylor, Chan, Chan et al., Sun and Schwartz is discussed above. Dousseau does not cure the deficiencies of this combination. The teachings of Dousseau are also discussed above.

In combining Dousseau with Taylor, Chan, Chan et al., Sun and Schwartz, the Examiner is suggesting that a water profile be subtracted from the profiles of the latter references. The

rejected claims recite the subtraction of mirror image peak profiles and/or peak profiles, and not water profiles, from sample population profiles. The combination of these references therefore does not yield the limitations of the rejected claims. Moreover, as stated above, there is no reason for combining the water subtraction method of Dousseau with the other references. Dousseau subtracts the water spectra in order to reduce noise and overcome user bias. There is no teaching in Taylor, Chan, Chan et al., Sun or Schwartz that signals are even detected from water and/or that any user bias exists in their respective methods. In addition, subtraction of a peak profile and/or a mirror image peak profile from a sample population profile serves to subtract polymer profiles, rather than noise, from a population profile.

Therefore there exists no motivation or rationale for combining the references, no reasonable expectation of success in such combination (particularly given that there is no indication that water signals or spectra are a problem in the methods of Taylor, Chan, Chan et al., Sun and Schwartz), and the combination even if made properly does not result in each and every limitation of the rejected claims. For at least these reasons, the combination of Taylor, Chan, Chan et al., Sun, Schwartz and Dousseau does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Taylor, Chan, Chan et al., Sun, Schwartz, Dousseau and Sievert

Claims 42 and 43 are rejected as being unpatentable over Taylor, in view of Chan, Chan et al., Sun, and Schwartz as applied to claim 32-36 and 38 above, and further in view of Dousseau et al. as applied to claims 40-41 above, and further in view of Sievert (EP0437829).

The combination of Taylor, Chan, Chan et al., Sun, Schwartz and Dousseau et al. is discussed above, as is the lack of a prima facie showing in view of these references. Sievert does not cure the deficiencies in the combination of Taylor, Chan, Chan et al., Sun, Schwartz and Dousseau.

Sievert reports methods for distinguishing between two mixtures of chemical compounds using chromatographic and spectrographic data. Sievert states that its methods are applicable to "chromatograms produced by other well known methods, such as gas chromatography and liquid techniques other than HPLC, such as capillary zone electrophoresis." (See page 8 lines 38-38-41.) These approaches serve to separate components within the mixture (see page 2 lines 26-28)

and thus yield profiles similar to those reported by Taylor where each peak represents a different entity. Sievert does not contemplate analysis of polymers labeled with sequence specific markers or the manipulation of intensity profiles obtained from individual polymers so labeled. Sievert contemplates subtraction of profiles of known mixtures of chemical entities (or standards) in order to identify the chemical components or to determine the complexity in a test mixture. The rejected claims require subtraction of profiles contained within the sample population profile itself. Sievert does not provide this teaching, among others.

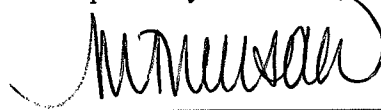
There exists no motivation or rationale for combining the references, no reasonable expectation of success in such combination, and the combination even if made properly does not result in each and every limitation of the rejected claims. For at least this reason, the combination of references does not render obvious the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C0989.70045US01.

Respectfully submitted,



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Docket No.: C0989.70045US01

Date: May 26, 2009